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Mechanical and *in vitro* evaluation of an experimental canine patent ductus arteriosus occlusion device

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Abstract

Patent ductus arteriosus (PDA) is a congenital cardiovascular malformation in which a fetal connection between the aorta and pulmonary artery remains patent after birth. This defect commonly results in clinical complications, even death, necessitating closure. Surgical ligation is the most common treatment but requires a thoracotomy and is therefore invasive. A minimally invasive option is preferable. A prototype device for PDA occlusion which utilizes shape memory polymer foams has been developed and evaluated using mechanical and *in vitro* experiments. Removal force and radial pressure measurements show that the prototype device exhibited a lower removal force and radial pressure than a commercially available device. The *in vitro* experiments conducted within simplified and physiological PDA models showed that the prototype does not migrate out of position into the pulmonary artery at either physiological or elevated pressures in multiple model configurations. While the radial pressure and removal force were lower than commercial devices, the device performed acceptably in the *in vitro* benchtop experiments warranting further prototype development.

Keywords

Patent ductus arteriosus; ACDO; Shape memory polymer

1. Introduction

The ductus arteriosus (DA) is a normal fetal connection between the aorta and main pulmonary artery (MPA). During the fetal development, the function of the DA is to shunt blood flow around the developing, but uninflated lungs. It remains open during development due to low oxygen tension (Heymann and Rudolph, 1975) and the circulation of vasodilators (Coceani and Olley, 1973; Hamrick and Hansmann, 2010; Michelakis et al., 2000). After birth, oxygen tension greatly increases and the production of vasodilators decreases, causing the DA to constrict and close (Leonhardt et al., 2003; Schneider and Moore, 2006).

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However, in some cases, the DA does not close, resulting in a condition known as patent ductus arteriosus (PDA). The residual communication between the two arteries leads to continuous left-to-right shunting of blood between the descending aorta to the MPA. This loading can result in substantive cardiac remodeling and numerous clinical manifestations including cardiac arrhythmias, congestive heart failure, ventricular dilation, mitral valve regurgitation, pulmonary over-circulation, and death (Achen et al., 2008; Nguyenba and Tobias, 2008). This defect affects 6.8 in 1000 canine births accounting for 28% of all congenital cardiac malformations, making it the most common congenital cardiac defect found in dogs (Patterson, 1968). When left uncorrected, the one-year mortality rate for this defect is 65% (Eyster et al., 1976), necessitating closure.

Traditionally, surgical ligation of the PDA *via* thoracotomy has been the accepted treatment for PDA in canines (Birchard et al., 1990; Eyster et al., 1976; Jackson and Henderson, 1979; Nguyenba and Tobias, 2008). However, this highly invasive surgery results in operative mortality rates from 0–11% (Birchard et al., 1990; Bureau et al., 2005; Eyster et al., 1976; Goodrich et al., 2007; Stanley et al., 2003; Van Israel et al., 2002) and risks of major complications such as nonfatal hemorrhage, pneumothorax, and chylothorax are 11–15% (Bureau et al., 2005; Goodrich et al., 2007; Stanley et al., 2003; Van Israel et al., 2002), increases the appeal of a viable minimally invasive treatment method (Tobias and Stauffer, 2010).

The first intravascular treatment of PDA in the dog was reported in 1994 (Miller et al., 1994). Since this initial report there have been studies investigating the viability of treating canine PDA with endovascular delivered occlusion devices intended for human use, such as embolization coils, the Amplatzer™ Vascular Plug (AVP), and the Amplatzer™ Ductal Occluder (ADO). While these had varying success, there were still issues present such as, completeness of occlusion, device migration, delivery system size, and ease of delivery (Achen et al., 2008; Campbell et al., 2006; Glaus et al., 2002; Gordon and Miller, 2005; Hogan et al., 2006; Singh et al., 2012; Sisson, 2003; Tanaka et al., 2007; Tobias and Stauffer, 2010).

The Amplatzer® Canine Ductal Occluder (ACDO) (Infiniti Medical, LLC, Menlo Park, CA), designed to address limitations of other endovascular treatments, was the first device designed to specifically conform to the canine PDA morphology (Nguyenba and Tobias, 2007, 2008) and is currently the most widely used device to close PDA in dogs. The device is a dense, self-expanding nickel titanium (nitinol) mesh which consists of a distal disk, used for positioning against the MPA ostium, a narrow waist which is placed within the minimal ductal diameter (MDD), and a proximal, cupped disk that helps stabilize the device within the PDA (Nguyenba and Tobias, 2007). Clinical studies have shown the ACDO to be very effective at occluding PDA, with 70–75% showing complete occlusion acutely upon implantation and up to 97–100% at 24 h (Gordon et al., 2010; Nguyenba and Tobias, 2008; Singh et al., 2012). However, while effective, this device is very expensive and cost prohibitive to some dog owners, pushing the cost of transvascular occlusion to approach and even exceed the cost of surgical ligation. Additionally, the size of the delivery system necessary for large ACDO's can reduce the number of patients that can be treated with this device (Gordon et al., 2010). Canine PDA size is not associated with age or body weight

(Miller et al., 2006), therefore, a small dog (<4 kg) may have a large PDA that cannot be treated because of the large delivery system required (Tobias and Stauthammer, 2010). Therefore, there is a clinical need to develop a device addressing these issues.

A prototype device which utilizes shape memory polymer (SMP) urethane foams has been developed for endovascular PDA treatment. Shape memory polymers are a class of material which can be heated above a characteristic glass transition temperature (T_g), deformed, cooled below the T_g setting it into a temporary shape, and actuated by increasing the polymer's temperature above the T_g via an external stimulus, such as heat, to return to their original shape (Lendlein and Kelch, 2002). These materials have been proposed for several biomedical device applications including use as embolic agents for endovascular occlusion (Maitland et al., 2007; Small et al., 2010). The ability of the foam to be delivered, compressed, and actuated to its original volume lends itself well to endovascular device delivery. Singhal et al. (2012) have demonstrated ultra-low density SMP foams with up to 70× volume expansion, 97–98% shape recovery after multiple cycles, and sharp, tailorable transition temperatures between 45–70 °C. In addition, the foams have shown excellent biocompatibility *in vitro* and *in vivo*, exhibiting the recruitment of collagen and connective tissue to form stable scar tissue, as well as clot formation within two minutes (Rodriguez et al., 2014a, 2014b, 2012; Singhal et al., 2012).

The goal of the present research is to develop an effective prototype PDA occlusion device with an equal or lower profile delivery system and with a lower cost than the ACDO. Decreasing the delivery profile of both small and large devices will allow clinicians to treat a greater population of dogs using minimally invasive techniques. Secondly, as the ACDO has become cost prohibitive, we have attempted to minimize the cost through reduction of materials used.

For the device to be successful, it must conform to multiple design requirements, including that the device must: be retractable back into the catheter/sheath after delivery, be deliverable through a 4Fr sheath with 1.3 mm inner diameter (ID) or smaller, occlude/reduce flow through the PDA to hemodynamically insignificant levels (Singh et al., 2012; Swensson et al., 1986), remain stable and not migrate once placed into the PDA, and be visible under fluoroscopy. These criteria will be evaluated in multiple mechanical and *in vitro* studies, which include radial pressure and removal force measurements, device stability and flow reduction measurements at physiological and elevated pressure gradients, and delivery into a physiologically representative model under fluoroscopy. Additionally, the mechanical properties and characteristics of the prototype device were compared to the properties of the ACDO.

2. Methods

PDA occlusion prototypes were fabricated using a custom process and then evaluated with mechanical and *in vitro* benchtop studies. Experiments performed included measuring the radial pressure the devices imparted on the vessel wall, measuring the force required to remove the device once positioned within the ductus, and evaluating device stability when subjected to physiological and elevated pressure gradients in simplified and physiologically

representative *in vitro* models. These methods enable evaluation of the efficacy of the current prototype and how to approach further development of this design.

2.1. Device fabrication

A monolithic nitinol foam cage (NFC), composed of a self-expanding nitinol frame and an SMP foam, was manufactured by laser cutting slots into a thin walled nitinol tube (NDC Inc, Fremont, CA) using a 248 nm excimer laser (Resonetics, Nashua, NH) outputting approximately 100 mW of power. The part was then deburred using abrasive paper and sonicated in isopropyl alcohol, followed by a heat treatment process to set the shape.

The shaping process is detailed in Fig. 1. First, stainless steel (SS) collars are positioned over the struts to prevent fracture formation during strut expansion, and a gauge pin was placed within the lumen of the tube to keep the device axial during the compression process, shown in Fig. 1A. A SS spacer was placed inside the unexpanded proximal struts to aid in the shaping of the rectangular geometry as shown in Fig. 1B, and positioned onto the fixture. The device was compressed axially to expand the proximal (Fig. 1C) and distal cages (Fig. 1D); an external frame restrained the proximal cage, setting its shape. The device and fixture was then heat treated at 550 °C for seven minutes in a furnace and subsequently quenched in room temperature water.

After the frame was created, a threaded detachment SS tube and nitinol backbone wire were attached. The backbone, constructed using 0.010 in. nitinol wire (NDC Inc, Fremont, CA) welded to a SS hypotube, was laser welded to the lumen of the threaded detachment tube using an iWeld 990 (Laser-Star, Riverside, RI), and this assembly was laser welded within the proximal lumen of the nitinol device frame.

The SMP foam composition used in these devices was the 0TM composition described and synthesized in a similar way to those reported by Singhal et al. (2013). These foams were chosen for their rapid expansion in water (~2 min in 37 °C water) (Singhal et al., 2013) allowing for fast occlusion of the PDA ductus, similar to the occlusion times of the ACDO (5–20 min) (Gordon et al., 2010; Singh et al., 2012). These foams were post processed following the protocol described by Hasan et al. (2014). Foam cylinders 6 mm diameter and 4 mm long were cut from the cleaned foams using surgical biopsy punches and crimped over 0.010 in. nitinol wire using a radial crimping head (Machine Solutions, Flagstaff, AZ) to a diameter less than the nitinol tube inner diameter (ID). The compressed foams were threaded from the nitinol wire onto the device backbone wire within the proximal cage. Fig. 2 shows a comparison of the ACDO to the NFC.

2.2. Model fabrication

Four different models were constructed for device testing based upon PDA geometric classification as described in Miller et al. (2006). These included three simplified models (IIA, IIB, and wide ampulla (WA) taper), and a physiologically representative model of canine PDA. The dimensions and shapes of the simplified models are shown in Fig. 3 and are based upon published data reported in Miller et al. (2006). The IIA and IIB models emulate the most common types of canine PDA morphology, and the WA model, based upon the IIA taper, was used to evaluate device performance when the device struts did not

contact the vessel wall due to ampulla, the portion of the ductus proximal to the MDD, expansion (Achen et al., 2008; Miller et al., 2006; Saunders et al., 2007).

Simplified PDA models were created by 3D printing the PDA geometries, casting polydimethylsiloxane (PDMS) around the 3D printed model, and dissolving the printed material, leaving the vessel geometry.

The physiologically representative vessel geometry was modeled using a computed tomographic angiogram (CTA) of a canine PDA. The surfaces of the descending aorta and MPA were extracted and sectioned using a trial version of Amira 3D analysis software (FEI Visualization Sciences Group Burlington, MA). Because the CTA provided was an unusual morphology, the geometry was modified to resemble a more typical IIA taper. The extracted volume was then imported into Solidworks (Dassault Systemes, Waltham, MA) for further processing and manufactured in a similar manner to the simplified PDA models using PDMS.

2.3. Radial pressure

Radial pressure applied to the vessel wall by the device was measured to ensure that the device would not impose severe vessel trauma or ampulla rupture. Experiments were performed using an Instron 5965 Test Frame (Instron, Norwood, MA) and Blockwise RJ62 J-Crimp™ Radial Compression Station (Blockwise Engineering LLC, Tempe, AZ), as shown in Fig. 4A and B. The Blockwise employs a linear relationship between the positions of the extension arm and the diameter of the compression station shown below as,

$$\Delta D = 0.7374 \cdot \Delta x, \quad (1)$$

where D is the change in diameter and x is the change in vertical position, and between the measured load seen by the extension arm and the radial force exerted by the device as,

$$TRF = 2.712 \cdot F, \quad (2)$$

where TRF is the total radial force and F is the force measured by the load cell. The TRF can be converted to radial pressure using,

$$P = \frac{TRF}{Strut SA}, \quad (3)$$

where $Strut SA$ is the surface area of the struts in contact with the Blockwise. To estimate the surface area of the ACDO in contact with the vessel wall, the ACDO was placed on a uniaxial tensile tester and elongated such that the diameter of the elongated ACDO was approximately the same as the vessel diameter to be tested. Images were captured and length measurements were conducted using ImageJ software (NIH, Bethesda, Maryland). These measurements were then used to estimate the surface area.

The radial pressure of the NFC and a 6 mm ACDO (sized at the device waist) was measured at five different diameters, 3.3, 4, 5, 5.5, and 6 mm, to simulate the device being deployed in different sized vessels. Prior to each run, the 50 N load cell was balanced. A baseline measurement was recorded for each diameter and was subtracted from each data set. Force measurements were recorded at a rate of 10 Hz for 30 s. Three NFC devices were tested at each diameter, and each test was conducted at least three times for each device. A single ACDO was tested at least three times at each diameter. The distal cage/disk of the NFC devices and ACDO was constrained during each of these tests with a Teflon tube, (Fig. 4C), allowing only the proximal cage to expand, because it would not exert force on vessel walls radially *in vivo*.

The radial pressure exerted by the devices was compared to the estimated burst pressure of the PDA vessel calculated using,

$$P = \frac{2st}{d_0}, \quad (4)$$

where P is radial pressure, s is the ultimate material strength, t is wall thickness, and d_0 is outer diameter of the vessel. From this method, the approximate burst pressure of the canine aorta was calculated as 200 kPa (1500 mmHg) (Cohen et al., 1972; Moriwaki et al., 2011).

2.4. Removal force

Experiments measuring the removal force were carried out using an MTS Synergie 400 tensile tester (MTS, Eden Prairie, MN). During experimentation, the devices were deployed into simplified PDA models and submerged within an isothermal water bath held at 37–38 °C. The distal end of each device was attached to the MTS gripper and was extended at 2.5 mm/min until it was pulled through the MDD. Force was recorded at a rate of 10 Hz. Three NFC devices and an ACDO were tested in each simplified PDA geometry. To assess repeatability, each NFC device frame was tested using three different foams (each 6 mm diameter × 4 mm long) as the foam is removable from the nitinol frame. The ACDO device was tested in each geometry at least three times. The removal force was recorded as the force required to dislodge the device from its implanted position, such that the proximal cage/disk protruded into the MPA.

2.5. Device stability and flow reduction in simplified in vitro models

The goal of this test was to determine whether the NFC device could withstand physiological and elevated pressure gradients and the amount of device migration and flow reduction when positioned into the previously described simplified PDA models.

2.5.1. Flow setup—A flow system was constructed and a representative schematic is shown in Fig. 5. Pressure gauges were placed proximally and distally to the PDA models to allow for measurement of the pressure gradient across the device. A water bath was used to hold the flow loop at 38 °C, emulating the canine body temperature (Eldredge et al., 2007). In order to control the pressure gradient across the ductus, a Y connector was placed prior to the PDA and a bypass arm was added. By adjusting the flow rate of the pump, the pressure

gradient across the device could be controlled. A hemostasis valve was used to introduce the delivery sheath into the flow loop to the model geometry.

2.5.2. Device preparation and delivery—NFC devices were prepared with compressed, 6 mm wide, 4 mm long foams prior to experimentation. NFC and ACDO devices were delivered through a 4Fr sheath (Cook Medical, Bloomington, IN). The sheath was advanced through the ductus and the device's distal cage was deployed under a no flow condition. The sheath was then retracted such that the distal cage was then in contact with the modeled pulmonic ostium of the ductus. The proximal cage was then unsheathed, deploying the device. After the device was fully advanced out of the sheath, the delivery cable was rotated counter-clockwise to unscrew the cable from the device. Following release, the sheath and delivery cable were retracted out of the flow loop and the foam was allowed to fully expand.

2.5.3. Device stability tests—Once the device was positioned and foam expanded (~1–5 min), the pump was turned on and the flow rate was set such that the pressure gradient across the PDA was approximately 100 mmHg (13.3 kPa) corresponding to the typical physiological pressure gradient across the ductus (Kittleson and Kinele, 1998; Singh et al., 2012). The flow rate was then held constant and images of the device and the pressure gradient were recorded every minute for five minutes. Following the test at 100 mmHg, the flow rate from the PDA arm of the flow loop was measured. Following the flow measurement, the systemic flow rate was increased to obtain a pressure gradient across the ductus of approximately 300 mmHg (40 kPa) to act as a safety factor, and the image and flow rate collection procedure described above was completed. After collection of the final flow rate, the device was removed and the un-occluded flow rate was collected for the flow speed used at each pressure gradient. Three different NFC devices were used and subjected to these tests three times in each of the PDA models for a total of twenty seven tests. One 6 mm ACDO was tested three times in each of the PDA models. The ACDO was only evaluated at the physiological pressure gradient.

Following the tests, device migration was assessed by measuring the length the distal end of the device moved relative to the MPA wall at zero (baseline), five (100 mmHg), and ten minutes (300 mmHg) by importing the collected images into ImageJ image analysis software.

2.6. Physiological model in vitro experimental setup

An *in vitro* test was conducted within the Texas Institute of Preclinical Studies (TIPS) facility at Texas A&M with the goal of obtaining clinician feedback regarding the ease of delivery/use of the NFC compared to the ACDO when deployed into a physiologically representative model under fluoroscopy. The primary tests that were conducted included evaluating device stability, retractability, and flow reduction.

2.6.1. Device preparation—Four NFC devices and a 6 mm ACDO device were used in this experiment. Table 1 below describes the device variants used.

The 4.5 mm OD distal cage type NFC design was tested in the simplified *in vitro* studies, and the 6 mm OD distal cage design was a variation used to test its ease of delivery when positioning compared to the smaller distal cage devices. The different sized foams were tested to monitor how foam diameter influenced flow reduction. The tungsten-doped foam device was tested to evaluate visibility under fluoroscopy compared to the non-radiopaque foams (Rodriguez et al., 2012).

2.6.2. Device delivery—The same flow loop used for device stability measurements in Section 2.5.1 was used for these tests. Devices (Table 1) were preloaded into polytetrafluoroethylene (PTFE) tube introducers and loaded through a check-flow valve at the end of the 4Fr sheath by a veterinary cardiologist (Dr. Matthew W. Miller) and advanced to the model geometry under fluoroscopic guidance. Devices were deployed in a similar manner as described in Section 2.5.2. Following deployment, the pressure gradient across the device was increased to 100 mmHg (13.3 kPa) by increasing the systemic flow rate and radiographic contrast was injected into the flow loop to qualitatively assess flow reduction. Additionally, when NFC 4 was implanted, the pressure gradient was increased to 200 mmHg (26.7 kPa), which can occur acutely, and contrast was injected to evaluate flow reduction.

2.6.3. Device retraction—Device retraction was performed on NFC 3 by the physician by pulling on the delivery cable in an attempt to recapture the delivered device into the sheath.

3. Results

3.1. Radial pressure

The average radial pressure exerted by each device at each diameter is shown in Fig. 6. Radial pressure for the ACDO and NFC decreased as the ampulla diameter increased. The pressure exerted on the wall by the ACDO was approximately equal to that of the NFC at ampulla diameters smaller than 5 mm, but was higher at ampulla diameters of 5.5 mm and 6 mm. The peak pressure exerted on the wall by the ACDO was 36 kPa (270 mmHg). The peak pressure exerted by the NFC was 33 kPa (247 mmHg). All NFC and ACDO devices tested exerted pressures below the calculated canine aorta burst pressure of 200 kPa (1500 mmHg).

3.2. Removal force

Fig. 7 shows the average removal force of the NFC and ACDO devices in each of the three simplified PDA geometries tested. The average removal force of the ACDO was higher than that of the NFC across all geometries tested. The average removal force was lowest for both the NFC and ACDO in the IIB geometry. The removal force of the NFC in the wide ampulla model was similar to that of the IIA model.

3.3. Simplified *in vitro* testing

3.3.1. Device stability—Fig. 8 shows representative images of the devices after deployment in the *in vitro* benchtop studies, after five minutes at 100 mmHg, and after five minutes held at 300 mmHg. The average migration was measured and calculated at these

time points and is shown in Table 2. There was additional migration after the pressure gradient was increased to 300 mmHg. The ACDO did not exhibit observable migration in any models tested.

The devices in the IIA taper exhibited the most axial migration (Fig. 8A). The proximal cages would slide in the ampulla when subjected to physiological pressures before contacting the MDD taper. The devices would slightly rotate in the IIB model at the elevated pressure gradient as shown in Fig. 8B. The devices remained in position relatively well at the 100 mmHg pressure gradient (B.2), but would slip and the device would slightly rotate at the 300 mmHg pressure gradient (B.3). The lowest migration was seen in the wide ampulla model (Fig. 8C). The struts were fully deployed and rested on the flat MDD taper. The devices were able to remain in position in the ampulla without applying outward pressure to the vessel walls.

3.3.2. Flow reduction—Flow through the PDA arm was measured with and without a device present at the physiological and elevated pressure gradients. The percent reduction in flow for each pressure and model is shown below in Table 3. NFC flow reduction was similar across each model for a given pressure gradient. Flow was impeded to the greatest extent by the NFC in the IIA model at both the physiological and elevated pressure gradients. The ACDO exhibited negligible flow reduction.

3.4. Physiological model in vitro experimentation

3.4.1. Device deployment—The NFC devices were delivered to the geometry without difficulty. Fig. 9 shows images from the deployment of NFC 1 (Table 1). Fig. 9A shows the NFC being advanced through the catheter to the MPA, Fig. 9B shows the distal cage deployed, Fig. 9C shows the distal cage pulled against the pulmonic ostium, and Fig. 9D shows the entire device deployed. The NFC conformed well to the ductus and remained securely in position, even when the delivery cable compressed the proximal cage during deployment and release. It was noted that the NFC was much easier to advance through the sheath compared to the ACDO.

NFC 3 was easier to deliver than NFCs 1 and 2, due to the larger distal cage. NFC 4 showed improved visualization due to the use of the tungsten doped foam. The clinician was able to visualize the foam expansion as a reduction in contrast, as shown in Fig. 10.

3.4.2. Device retraction—NFC retraction into the sheath was assessed using NFC 3 (Table 1). The device was deployed as previously described in Section 2.5.2 and after the foam was fully expanded, NFC retraction was attempted while at a physiological pressure gradient of 100 mmHg. The clinician successfully retracted the device into the 4Fr sheath by holding the sheath in place and pulling the device cable to recapture the device.

3.4.3. Occlusion—The post deployment angiograms of NFCs 1, 2, 4, and the ACDO (Table 1) were compared to assess completeness of occlusion. Since no blood was present, the foam could not completely occlude the ductus with thrombus formation, however, flow reduction was expected. Fig. 11 shows images of the devices within the model during angiograms.

The foam of NFC 1 (Fig. 11C) did not show appreciable flow reduction as the angiogram appeared similar to the baseline angiogram. It appears that NFCs 2 and 4 provided the best occlusion as indicated by the amount of contrast present in the ampulla during the angiogram (Fig. 11D and F). The contrast was slowest to clear in Fig. 11F, when the pressure gradient was set to 200 mmHg. The ACDO showed similar flow reduction to the small foam NFC as indicated by the lighter contrast (Fig. 11B and C); NFC's with larger and denser foams show darker contrast on the side of contrast delivery (Fig. 11D–F).

4. Discussion

4.1. Radial pressure

The ACDO exerted a higher pressure than the NFC at all ampulla diameters tested except at 4 mm. The ACDO exerted a higher pressure than the NFC because the OD of the ACDO was 11 mm whereas the OD of the NFC was 6.3 mm (Fig. 6). Additionally, the ACDO pressure may be underestimated as the proximal cup shape and waist could not be fully deployed into our test system as it would be deployed *in vivo*.

The devices were tested at a range of vessel sizes to determine how the pressure exerted on the wall changed as a function of vessel diameter to ensure that the pressure exerted by an oversized device placed into a small PDA would not burst the vessel. The NFC is designed to be deployed in a PDA with a 5.5–6 mm ampulla, and an MDD of 3 mm. At these diameters, the device exerts approximately 2–11 kPa (15–80 mmHg) of pressure, which is much lower than the pressure exerted by the ACDO (16–17 kPa, 120–128 mmHg) and the calculated burst pressure of 200 kPa (1500 mmHg).

As indicated by the wide ampulla migration studies, radial pressure may not directly correlate to device stability. The oversized device waist and ability for the device to catch on a ductal taper are more important factors when predicting stability. The ACDO has been used to treat tubular PDAs without a ductal taper, but caution is urged when treating this shape because stability only comes from oversizing the device relative to the PDA diameter (Nguyenba and Tobias, 2008). The NFC was found to exert pressures much lower than the estimated vessel burst pressure and on the same order of magnitude as the ACDO (Fig. 6), which indicates that the current NFC design minimizes vessel trauma and the risk of ampulla rupture due to deployment pressure.

4.2. Removal force

The removal force of the ACDO was approximately six times higher than that of the NFC in all models tested (Fig. 7). The cupped proximal disk and oversized waist of the ACDO increased the device stability and force required to remove it from position, resulting in no visible migration of the device in the *in vitro* tests. Therefore, it was concluded that higher removal forces correspond to increased device stability and reduced migration.

The removal force of the NFC was underestimated as the experiment only evaluated the removal force of the device frame, even with the presence of foam in the device. In the *in vitro* experiments, the flow compressed the foam against the struts, keeping them flat against the taper of the ampulla, helping the entire device remain in position. In the removal force

experiment, flow was not present and the foam was not compressed against the NFC struts. The removal force was lowest in the IIB model because the angled taper of the rigid model did not allow the devices to fully expand; therefore, the struts were already partially collapsed. The removal force was highest in the WA model because the devices were allowed to fully expand, increasing the amount of force required to collapse the struts into the MDD. These experiments would be more representative of *in vivo* conditions if thin walled PDMS models were used instead of the rigid, thick walled models used.

4.3. Simplified model in vitro experiments

4.3.1. Device stability—Device migration and rotation is not desirable, but it was promising that the proximal cage and foam were not forced through the ductus. There was only one instance in which the struts on the proximal cage partially compressed into the MDD, but the device was not completely forced into the MPA. However, while it is optimal to minimize device protrusion into the MPA, minimal device protrusion has not been reported to cause clinical complications (Sreeram et al., 1999). The ACDO did not exhibit visible migration once positioned, as has been reported in multiple *in vivo* studies (Nguyenba and Tobias, 2008; Singh et al., 2012).

The NFC migration could be due to the rigid PDMS model and fabrication methods used. A thin walled model would more accurately mimic a compliant blood vessel and allow the device to fully expand and remain anchored in place. While no migration is desired, these initial results are promising and can be improved with future designs by modifying the cage. Decreasing the distance between the proximal and distal cages would allow the proximal and distal cages to better compress the tissue around the MDD.

4.3.2. Simplified model flow reduction experiments—The NFC reduced flow by approximately 50% at the physiological pressure gradient and approximately 80% at the elevated pressure gradient (Table 3). It was not expected that the device would achieve 100% occlusion in the absence of blood. The goal of the test was to ensure that flow was being impeded. It has been reported that when similar SMP foams have been placed within blood vessels, clotting and complete occlusion of the blood vessel occurs in approximately two minutes (Rodriguez et al., 2014b). The NFC reduced flow to a much greater extent compared to the ACDO, which showed negligible reduction. ACDO flow reduction at 300 mmHg could not be assessed as the device did not impede flow enough to allow our system to develop this pressure drop. Despite the negligible reduction of flow in water, the ACDO performs very well when implanted clinically (Gordon et al., 2010; Nguyenba and Tobias, 2008; Singh et al., 2012). Therefore, as evidenced by the reduction of flow in water and results from Rodriguez et al., the NFC should rapidly occlude the defect on a similar or faster timescale compared to the ACDO (~5 to 20 min) (Gordon et al., 2010; Singh et al., 2012).

4.4. Physiological in vitro experiments

The overall response regarding the NFC from the veterinary cardiologist was very positive. The veterinary cardiologist commented that the deployment of the NFC devices offered easy delivery and effortless advancement through the delivery sheath, and was much easier to

advance and exhibited much less resistance than the ACDO. The 6 mm ACDO used in this test is designed to be deployed through a 5Fr sheath, however, it was delivered through a 4Fr sheath per standard clinical use (Nguyenba and Tobias, 2007). It is desirable to deliver the devices through smaller delivery sheaths because it expands the population of patients that can be treated (Sisson, 2003; Tobias and Stauthammer, 2010). The delivery time of the NFC was similar to that of the ACDO, meaning that the patient and clinician would not be subjected to a larger radiation dose than the current method due to increased procedure time. All NFC devices were properly deployed. Similar to the ACDO devices, the NFC was easily recaptured into the delivery sheath when repositioning was attempted. Therefore, the device could be retracted if there was an undesirable placement in the clinic. The ACDO did not appear to occlude flow as well as the NFC as indicated by the lighter contrast (Fig. 11B). However, none of the devices exhibited complete occlusion because the blood clotting capabilities were not present.

5. Conclusions

The ACDO is an effective device for canine PDA occlusion, however, its large delivery system and expense limits its use in the clinic. An option that is deliverable in an equal or lower profile system with similar mechanical and occlusion properties and lesser cost is desirable.

The NFC conformed to the proposed requirements, and performed similarly to the ACDO in our tests. One area in which it shows improvement is its scalable aspect. The NFC cage diameter can be adjusted by increasing the length of the laser cut slots, thereby altering its expanded diameter, making it capable of treating large and small PDAs through a 4Fr sheath. The compressed OD is limited to the OD of the nitinol tube or compressed SMP, whichever is larger. Some ACDOs are deliverable in sheaths this size, but not those used to treat larger geometries. Additionally, using a smaller OD nitinol tube may allow for the treatment of canine PDA through even smaller delivery systems such as 4Fr catheters (OD ~1.3 mm), further expanding the population of patients that could be treated with the NFC.

The NFC was designed to minimize materials used with the goal of reducing the cost compared to the ACDO. The NFC frame is formed from 1.25 in. of 0.044 in. OD, 0.041 in. ID nitinol tubing, and the ACDO's frame is composed of two or three 144, 0.0015–0.003 in. nitinol wires (Nguyenba and Tobias, 2007). The cost of the SMP foam is negligible. The NFC minimizes materials needed for stability and occlusion (monolithic nitinol frame and SMP foam), compared to the hundreds of wires required for the ACDO. However, while we have shown a reduction of materials used in fabrication, there are other factors that contribute to device cost, such as manufacturing processes and preclinical testing costs that will be analyzed in future studies.

The current NFC design is dependent upon the ability for the device to fully expand rather than to apply pressure to the vessel wall, as it appeared most stable in the WA model. This is encouraging because even if there is ampulla enlargement post deployment, it should not compromise the treatment as can occur with other endovascular treatment methods (Achen et al., 2008), further reducing the risk of complications during treatment.

The presented results and the promising clinician feedback obtained indicate that with design refinement, the NFC device could be used to treat canine PDA.

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Abbreviations

DA	Ductus arteriosus
MPA	Main pulmonary artery
PDA	Patent ductus arteriosus
AVP	Amplatzer™ Vascular Plug
ADO	Amplatzer™ Duct Occluder
ACDO	Amplatz® Canine Ductal Occluder
MDD	Minimal ductal diameter
SMP	Shape memory polymer
T_g	Glass transition temperature
NFC	Nitinol foam cage
SS	Stainless steel
WA	Wide ampulla
CTA	Computed tomographic angiogram

References

- Achen SE, Miller MW, Gordon SG, Saunders AB, Roland RM, Drourr LT. Transarterial ductal occlusion with the amplatzer vascular plug in 31 Dogs. *J Vet Intern Med.* 2008; 22:1348–1352. [PubMed: 18798793]
- Birchard SJ, Bonagura JD, Fingland RB. Results of ligation of patent ductus-arteriosus in Dogs – 201 Cases (1969–1988). *J Am Vet Med Assoc.* 1990; 196:2011–2013. [PubMed: 2365630]
- Bureau SP, Monnet E, Orton EC. Evaluation of survival rate and prognostic indicators for surgical treatment of left-to-right patent ductus arteriosus in dogs: 52 cases (1995–2003). *J Am Vet Med Assoc.* 2005; 227:1794–1799. [PubMed: 16342529]
- Campbell FE, Thomas WP, Miller SJ, Berger D, Kittleson MD. Immediate and late outcomes of transarterial coil occlusion of patent ductus arteriosus in dogs. *J Vet Intern Med.* 2006; 20:83–96. [PubMed: 16496927]
- Coceani F, Olley PM. The response of the ductus arteriosus to prostaglandins. *Can J Physiol Pharm.* 1973; 51:220–225.
- Cohen J, Litwin SB, Aaron A, Fine S. The rupture force and tensile strength of canine aortic tissue. *J Surg Res.* 1972; 13:321–333. [PubMed: 4652936]

- Eldredge, DM., Carlson, LD., Carlson, DG., Griffin, JM. Dog Owner's Home Veterinary Handbook. Wiley Publishing, Inc.; Hoboken, NJ: 2007.
- Eyster GE, Eyster JT, Cords GB, Johnston J. Patent ductus arteriosus in the dog: characteristics of occurrence and results of surgery in one hundred consecutive cases. *J Am Vet Med Assoc.* 1976; 168:435–438. [PubMed: 1254517]
- Glaus TM, Berger F, Ammann FW, Kiowski W, Ohlert S, Boller M, Kastner S, Reusch CE, Sisson D. Closure of large patent ductus arteriosus with a self-expanding duct occluder in two dogs. *J Small Anim Pract.* 2002; 43:547–550. [PubMed: 12489744]
- Goodrich KR, Kyles AE, Kass PH, Campbell F. Retrospective comparison of surgical ligation and transarterial catheter occlusion for treatment of patent ductus arteriosus in two hundred and four dogs (1993–2003). *Vet Surg.* 2007; 36:43–49. [PubMed: 17214819]
- Gordon SG, Miller MW. Transarterial coil embolization for canine patent ductus arteriosus occlusion. *Clin Tech Small Anim Pract.* 2005; 20:196–202. [PubMed: 16180402]
- Gordon SG, Saunders AB, Achen SE, Roland RM, Drouin LT, Hariu C, Miller MW. Transarterial ductal occlusion using the amplatzs canine duct occluder in 40 dogs. *J Vet Cardiol.* 2010; 12:85–92. [PubMed: 20615776]
- Hamrick SEG, Hansmann G. Patent ductus arteriosus of the preterm Infant. *Pediatrics.* 2010; 125:1020–1030. [PubMed: 20421261]
- Hasan SM, Raymond JE, Wilson TS, Keller BK, Maitland DJ. Effects of Isophorone diisocyanate on the thermal and mechanical properties of shape-memory polyurethane foams. *Macromol Chem Phys.* 2014; 215:2420–2429.
- Heymann MA, Rudolph AM. Control of ductus arteriosus. *Physiol Rev.* 1975; 55:62–78. [PubMed: 1088992]
- Hogan DF, Green HW, Sanders RA. Transcatheter closure of patent ductus arteriosus in a dog with a peripheral vascular occlusion device. *J Vet Cardiol.* 2006; 8:139–143. [PubMed: 19083347]
- Jackson WF, Henderson RA. Ligature placement in closure of patent ductus arteriosus. *J Am Anim Hosp Assoc.* 1979; 15:55–58.
- Kittleson, MD., Kinele, RD. *Small Animal Cardiovascular Medicine.* Mosby, Inc.; St. Louis, MO: 1998.
- Lendlein A, Kelch S. Shape-memory polymers. *Angew Chem Int Ed.* 2002; 41:2034–2057.
- Leonhardt A, Glaser A, Wegmann M, Schranz D, Seyberth H, Nusing R. Expression of prostanoid receptors in human ductus arteriosus. *Br J Pharmacol.* 2003; 138:655–659. [PubMed: 12598419]
- Maitland DJ, Small IVW, Ortega JM, Buckley PR, Rodriguez J, Hartman J, Wilson TS. Prototype laser-activated shape memory polymer foam device for embolic treatment of aneurysms. *J Biomed Opt.* 2007; 12:030504-030501–030504-030503. [PubMed: 17614707]
- Michelakis E, Rebeyka I, Bateson J, Olley P, Puttagunta L, Archer S. Voltage-gated potassium channels in human ductus arteriosus. *Lancet.* 2000; 356:134–137. [PubMed: 10963252]
- Miller MW, Gordon SG, Saunders AB, Arsenault WG, Meurs KM, Lehmkuhl LB, Bonagura JD, Fox PR. Angiographic classification of patent ductus arteriosus morphology in the dog. *J Vet Cardiol.* 2006; 8:109–114. [PubMed: 19083344]
- Miller, MW., Miller, KM., Boswood, A. Echocardiographic assessment of PDA after occlusion. *Proceedings of the 14th Annual Veterinary Forum, ACVIM; San Francisco, CA.* 1994. p. 305-306.
- Moriwaki T, Oie T, Takamizawa K, Murayama Y, Fukuda T, Omata S, Kanda K, Nakayama Y. Variations in local elastic modulus along the length of the aorta as observed by use of a scanning haptic microscope (SHM). *J Artif Organs.* 2011; 14:276–283. [PubMed: 21858475]
- Nguyenba TP, Tobias AH. The amplatz (R) canine duct occluder: a novel device for patent ductus arteriosus occlusion. *J Vet Cardiol.* 2007; 9:109–117. [PubMed: 18054306]
- Nguyenba TP, Tobias AH. Minimally invasive per-catheter patent ductus arteriosus occlusion in dogs using a prototype duct occluder. *J Vet Intern Med.* 2008; 22:129–134. [PubMed: 18289299]
- Patterson DF. Epidemiologic and genetic studies of congenital heart disease in the dog. *Circ Res.* 1968; 23:171–202. [PubMed: 5662573]

- Rodriguez JN, Clubb FJ, Wilson TS, Miller MW, Fossum TW, Hartman J, Tuzun E, Singhal P, Maitland DJ. In vivo response to an implanted shape memory polyurethane foam in a porcine aneurysm model. *J Biomed Mater Res A*. 2014a; 102:1231–1242. [PubMed: 23650278]
- Rodriguez JN, Miller MW, Boyle A, Horn J, Yang CK, Wilson TS, Ortega JM, Small W, Nash L, Skoog H, Maitland DJ. Reticulation of low density shape memory polymer foam with an in vivo demonstration of vascular occlusion. *J Mech Behav Biomed*. 2014b; 40:102–114.
- Rodriguez JN, Yu YJ, Miller MW, Wilson TS, Hartman J, Clubb FJ, Gentry B, Maitland DJ. Opacification of shape memory polymer foam designed for treatment of intracranial aneurysms. *Ann Biomed Eng*. 2012; 40:883–897. [PubMed: 22101759]
- Saunders AB, Miller MW, Gordon SG, Bahr A. Echocardiographic and angiographic comparison of ductal dimensions in dogs with patent ductus arteriosus. *J Vet Intern Med*. 2007; 21:68–75. [PubMed: 17338152]
- Schneider DJ, Moore JW. Patent ductus arteriosus. *Circulation*. 2006; 114:1873–1882. [PubMed: 17060397]
- Singh MK, Kittleson MD, Kass PH, Griffiths LG. Occlusion devices and approaches in canine patent ductus arteriosus: comparison of outcomes. *J Vet Intern Med*. 2012; 26:85–92. [PubMed: 22211471]
- Singhal P, Boyle A, Brooks ML, Infanger S, Letts S, Small W, Maitland DJ, Wilson TS. Controlling the actuation rate of low-density shape-memory polymer foams in water. *Macromol Chem Phys*. 2013; 214:1204–1214. [PubMed: 25530688]
- Singhal P, Rodriguez JN, Small W, Eagleston S, de Water JV, Maitland DJ, Wilson TS. Ultra low density and highly crosslinked biocompatible shape memory polyurethane foams. *J Polym Sci Part B – Polym Phys*. 2012; 50:724–737.
- Sisson D. Use of a self-expanding occluding stent for nonsurgical closure of patent ductus arteriosus in dogs. *J Am Vet Med Assoc*. 2003; 223:999–1005. [PubMed: 14552489]
- Small W IV, Singhal P, Wilson TS, Maitland DJ. Biomedical applications of thermally activated shape memory polymers. *J Mater Chem*. 2010; 20:3356–3366. [PubMed: 21258605]
- Sreeram N, Tofeig M, Walsh KP, Hutter P. Lung perfusion studies after detachable coil occlusion of persistent arterial duct. *Heart*. 1999; 81:642–645. [PubMed: 10336925]
- Stanley BJ, Luis-Fuentes V, Darke PGG. Comparison of the incidence of residual shunting between two surgical techniques used for ligation of patent ductus arteriosus in the dog. *Vet Surg*. 2003; 32:231–237. [PubMed: 12784199]
- Swensson RE, Valdesacruz LM, Sahn DJ, Sherman FS, Chung KJ, Scagnelli S, Hagenansert S. Real-time doppler color flow mapping for detection of patent ductus-arteriosus. *J Am Coll Cardiol*. 1986; 8:1105–1112. [PubMed: 3531287]
- Tanaka R, Soda A, Saida Y, Sugihara K, Takashima K, Shibazaki A, Yamane Y. Evaluation of the efficacy and safety of coil occlusion for patent ductus arteriosus in dogs. *J Vet Med Sci*. 2007; 69:857–859. [PubMed: 17827897]
- Tobias AH, Stauthammer CD. Minimally invasive per-catheter occlusion and dilation procedures for congenital cardiovascular abnormalities in dogs. *Vet Clin N Am – Small*. 2010; 40:581–603.
- Van Israel N, French AT, Dukes-McEwan J, Corcoran BM. Review of left-to-right shunting patent ductus arteriosus and short term outcome in 98 dogs. *J Small Anim Pract*. 2002; 43:395–400. [PubMed: 12238504]

Fig. 1. NFC shape setting procedure. (A) Laser cut nitinol tubing with SS spacers positioned and gauge pin placed within lumen. (B) Interior SS spacer positioned in proximal struts. (C) Tube is compressed axially so proximal cage opens. (D) Tube is compressed axially further to expand distal struts.

Fig. 2.
PDA device comparison. (A) 6 mm ACDO (sized at the device waist); (B) NFC, foam compressed; (C) NFC foam expanded. (Same scale across frames).

Fig. 3. Simplified PDA model geometries. Dimensions and shapes based upon common canine PDA shapes (Miller et al., 2006).

Fig. 4.

Radial pressure testing setup. (A) Blockwise RJ-A62 J-Crimp™ Radial Compression Station attached to Instron Test Frame. (B) Enlarged, front view of compression blades, set to 5 mm diameter, with NFC deployed. (C) Side view schematic of deployed NFC within compression station showing constrained distal cage.

Fig. 5.
Schematic of flow loop used for *in vitro* testing.

Fig. 6. Average radial pressure. Average radial pressure of the NFC compared to the ACDO at each ampulla ID tested.

Fig. 7. Average removal force. Average removal force of the NFC and ACDO for each simplified vessel geometry.

Fig. 8. Device stability in the IIA (A.1–A.3), IIB (B.1–B.3), and WA (C.1–C.3) models. Flow is from left to right. Images recorded after device subjected to labeled pressures for five minutes.

Fig. 9. NFC deployment (NFC 1) into physiological model under fluoroscopic guidance. (A) NFC in catheter. (B) Distal cage deployed from catheter. (C) NFC placement against pulmonic ostium of model. (D) Proximal cage delivered and device released. White arrow indicates distal cage during deployment and positioning.

Fig. 10.

Tungsten-doped foam visibility under fluoroscopic guidance during NFC 4 delivery. (A) NFC in catheter. (B) Proximal cage deployment, foam begins to expand. (C) NFC deployed, foam expansion indicated by reduction in the radiographic contrast of foam. White arrow indicates foam location.

Fig. 11.

Flow reduction comparison. Images were collected at the time when max contrast was present in ampulla as determined by visual inspection. (A) Model without a device present to provide a baseline image. (B) Model with the ACDO positioned. (C) and (D) NFC devices with a 6 mm diameter and 8 mm diameter SMP foam respectively. (E) and (F) NFC 4 subject to a 100 mmHg and 200 mmHg pressure gradient respectively.

Table 1

Physiological *in vitro* device list. Specifications of devices used in the physiological *in vitro* tests.

ID	Device variant	Expanded foam diameter
NFC 1	4.5 mm OD distal cage	6 mm foam
NFC 2	4.5 mm OD distal cage	8 mm foam
NFC 3	6 mm OD distal cage	6 mm foam
NFC 4	4.5 mm OD distal cage	6 mm tungsten-doped foam (Rodriguez et al., 2012)
ACDO	N/A	6 mm waist (designed to occlude 3 mm MDD)

Table 2

Device migration summary. NFC migration at physiological and elevated pressure gradients for each model tested.

Model morphology	NFC axial migration (mm)	
	100 mmHg	300 mmHg
IIA	0.7±0.3	1.1±0.4
IIB	0.1±0.2	0.8±0.2
WA	0.6±0.4	0.8±0.4

Table 3

Device flow reduction summary. Percent reduction of flow at the physiological and elevated pressure gradients.

Model morphology	NFC flow reduction		ACDO flow reduction
	100 mmHg	300 mmHg	100 mmHg
IIA	60%±5%	83%±2%	1%±0.2%
IIB	51%±7%	80%±5%	0.6%±0.06%
WA	58%±5%	78%±4%	0.7%±0.6%